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(54) Title: POWDER FORMULATIONS SUITABLE FOR INHALATION

(57) Abstract: The invention relates to powdered preparations containing tiotropium for inhalation, processes for preparing them as well as their use for preparing a pharmaceutical composition for treating respiratory complaints, particularly for treating COPD (chronic obstructive pulmonary disease) and asthma.

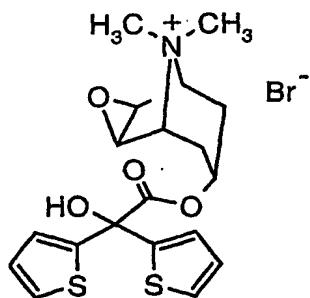
POWDER FORMULATIONS SUITABLE FOR INHALATION

The invention relates to powdered preparations containing tiotropium for inhalation, processes for preparing them as well as their use for preparing a pharmaceutical composition for treating respiratory complaints, particularly for treating COPD (chronic obstructive pulmonary disease) and asthma.

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10 (chronic obstructive pulmonary disease) and asthma.

Background to the invention

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and
10 has the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long-lasting activity which can be used to treat respiratory complaints, particularly COPD (chronic
15 obstructive pulmonary disease) and asthma. The term tiotropium refers to the free ammonium cation.

For treating the abovementioned complaints, it is useful to administer the active substance by inhalation. In addition to the administration of broncholytically active
20 compounds in the form of metered aerosols and inhalable solutions, the use of inhalable powders containing active substance is of particular importance.

With active substances which have a particularly high efficacy, only small amounts of the active substance are needed per single dose to achieve the desired therapeutic
25 effect. In such cases, the active substance has to be diluted with suitable excipients in order to prepare the inhalable powder. Because of the large amount of excipient, the properties of the inhalable powder are critically influenced by the choice of excipient. When choosing the excipient its particle size is particularly important. As a rule, the finer the excipient, the poorer its flow properties. However, good flow
30 properties are a prerequisite for highly accurate metering when packing and dividing up the individual doses of preparation, e.g. when producing capsules (inhalettes) for powder inhalation or when the patient is metering the individual dose before using a

- multi-dose powder inhaler. Moreover, the particle size of the excipient is very important for the emptying characteristics of capsules when used in an inhaler. It has also been found that the particle size of the excipient has a considerable influence on the proportion of active substance in the inhalable powder which is delivered for inhalation. The term inhalable proportion of active substance refers to the particles of the inhalable powder which are conveyed deep into the branches of the lungs when inhaled with a breath. The particle size required for this is between 1 and 10 µm, preferably less than 6 µm.
- 5 The aim of the invention is to prepare an inhalable powder containing tiotropium which, while being accurately metered (in terms of the amount of active substance and powder mixture released and delivered to the lungs by each inhalation process) with only slight variations between batches, enables the active substance to be administered in a therapeutically effective inhalable proportion.
- 10 The fact that tiotropium, particularly tiotropium bromide, has a therapeutic efficacy even at very low doses imposes further conditions on an inhalable powder which is to be used with highly accurate metering. Because only a low concentration of the active substance is needed in the inhalable powder to achieve the therapeutic effect,
- 15 a high degree of homogeneity of the powder mixture and only slight fluctuations in the dispersion characteristics from one batch to the next are essential. The homogeneity of the powder mixture and minor fluctuations in the dispersion properties are crucial in ensuring that the inhalable proportion of active substance is released reproducibly in constant amounts and with the lowest possible variability.
- 20 Accordingly, a further aim of the present invention is to prepare an inhalable powder containing tiotropium which is characterised by a high degree of homogeneity and uniformity of dispersion. The present invention also sets out to provide an inhalable powder which allows the inhalable proportion of active substance to be administered with the lowest possible variability. Furthermore, the present invention sets out to provide an inhalable powder being characterized by a high stability.
- 25
- 30

Detailed description of the invention

It was found that, surprisingly, the objective outlined above can be achieved by
35 means of the tiotropium containing powdered preparations for inhalation (inhalable powders) obtainable by the method according to the invention described hereinafter.

Accordingly, the invention relates to a method for preparing a physically stable and homogenous powdered preparation containing tiotropium in admixture with a

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physiologically acceptable excipient, characterized in that the tiotropium salt and the physiologically acceptable excipient are suspended in a suspending agent, in which the tiotropium salt and the physiologically acceptable excipient are essentially insoluble, and from the thus obtained suspension the suspending agent is removed.

5

Preferably the invention relates to a method for preparing a physically stable and homogenous powdered preparation containing tiotropium in an amount of 0.001 to 2%.

- 10 Preferably the suspending agent applied in the method according to the invention is selected from the group consisting of alkanes, alcohols, ketones, mixtures of alkanes with alcohols and mixtures of alkanes with ketones. Of particular interest are suspending agents selected from the group consisting of hexane, heptane, methanol, ethanol, and mixtures thereof. Within the scope of the invention
- 15 references to hexane or heptane are to be understood as references to all of the possible isomers. However, n-hexane and n-heptane, optionally in admixture with methanol or ethanol, preferably ethanol, are of particular interest. If mixtures of the aforementioned suspending agents are applied the amount of alkane is preferably at least 90 %, more preferably at least 95 %. Of particular interest within the scope of
- 20 the present invention are mixtures containing at least 98 % alkane. In a preferred embodiment the suspending agent is hexane, preferably n-hexane containing 1%, preferably 0.5 % ethanol. In another preferred embodiment the suspending agent is heptane, preferably n-heptane containing 1%, preferably 0.5 % ethanol.
- 25 By tiotropium is meant the free ammonium cation. The counter-ion (anion) may be chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate. Of these anions, the bromide is preferred. By the term tiotropium salt is meant the salt formed by the cation tiotropium and one of the aforementioned counter-ions (anions). Within the scope of the present invention, tiotropium bromide
- 30 is preferred of all the tiotropium salts.

- References to tiotropium bromide within the scope of the present invention should always be taken as references to all possible amorphous and crystalline modifications of tiotropium bromide. Surprisingly, it has been found that depending on the reaction conditions and solvent used during the process of preparation of tiotropium bromide, different crystal modifications of tiotropium bromide are obtained. Preferred according to the invention are those powder preparations, that contain tiotropium in form of the crystalline tiotropium bromide monohydrate. References to crystalline tiotropium bromide monohydrate within the scope of the present invention

should always be taken as references to the crystal modification described in more detail below.

- Another object of the invention concerns the tiotropium containing powdered
5 preparations obtainable by the method of preparation according to the invention.

In a preferred embodiment of the invention the powdered preparations contain 0.001 to 2 %, more preferably 0.01 to 1.5 % of tiotropium.

- 10 The percentages given within the scope of the present invention are always percent by weight if not indicated to the contrary.

Preferably the powdered preparations obtainable according to the invention contain 0.04 to 0.8% tiotropium. Powdered preparations obtainable according to the
15 invention which contain 0.08 to 0.64%, most preferably 0.1 to 0.4% of tiotropium, are particularly preferred according to the invention.

- As mentioned hereinbefore, tiotropium bromide is of particular interest within the
20 scope of the present invention. Accordingly, the powdered preparations obtainable according to the invention preferably contain 0.0012 to 2.41 %, more preferably 0.012 to 1.81 % of tiotropium bromide. Preferably the powdered preparations obtainable according to the invention contain 0.048 to 0.96% tiotropium bromide.
25 Powdered preparations obtainable according to the invention which contain 0.096 to 0.77%, most preferably 0.12 to 0.48% of tiotropium bromide, are particularly preferred according to the invention.

- Tiotropium bromide is, depending on the choice of reaction conditions and solvents, obtainable in different crystalline modifications. Most preferred according to the invention are those powder preparations, that contain tiotropium in form of the
30 crystalline tiotropium bromide monohydrate. Accordingly, the powdered preparations obtainable according to the invention preferably contain 0.0012 to 2.5 %, more preferably 0.0125 to 1.87 % of crystalline tiotropium bromide monohydrate.
35 Preferably the powdered preparations obtainable according to the invention contain 0.05 to 1.0% crystalline tiotropium bromide monohydrate. Powdered preparations obtainable according to the invention which contain 0.1 to 0.8%, most preferably 0.12 to 0.5% of crystalline tiotropium bromide monohydrate, are particularly preferred according to the invention.

- Examples of physiologically acceptable excipients which may be used to prepare the inhalable powders according to the invention include, for example, monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, 5 mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose or glucose are the particularly preferred excipient, while lactose monohydrate and glucose monohydrate 10 are most particularly preferred.

The active substance introduced into the method according to the invention has an average particle size of 0.5 to 10 μm , preferably 1 to 6 μm , most preferably 1.5 to 5 μm . This particle size is obtained by micronisation of the tiotropium salt according to 15 methods known in the art.

- The inhalable powders according to the invention are preferably characterised in that the excipient has an average particle size of about 20 to about 500 μm , more preferably of about 30 to about 300 μm , most preferably of about 40 to about 200 μm .
20 The phrase average particle size used here denotes the 50% value from the volume distribution measured with a laser diffractometer using the dry dispersion method.

The method according to the invention is described in more detail below.
In a first step tiotropium salt is weight into a mixing vessel. It is apparent for the 25 person skilled in the art that the amount of tiotropium salt added depends on the desired concentration of tiotropium in the final powder formulation. As mentioned hereinbefore the powdered preparations according to the invention preferably contain 0.001 to 2 % tiotropium. In the next step the suspending agent is added. Preferably such an amount of suspending agent is added that, after addition of all 30 powdered ingredients (active ingredient and excipient), the powder/liquid ratio of the suspension thus obtained is in a range of about 0.1 to about 2 g/ml, preferably of about 0.2 to about 1 g/ml, more preferably of about 0.25 to about 0.85 g/ml. In a further preferred embodiment the amount of suspending agent leads to a powder/liquid ration of about 0.4 to about 0.75 g/ml. According to one embodiment of 35 the invention the total amount of the suspending agent can be directly added. In a yet preferred embodiment according to the invention the suspending agent is added in at least two, preferably two portions, the first portion being added to the tiotropium salt, the second portion being added after addition of the excipient. If the suspending agent is added in two portions the first portion added is about 10 to 90 %, preferably

- 20 to 70 %, more preferably 30 to 60 % of the suspending agent used in total. After addition of the suspending agent the suspension thus obtained is stirred and optionally subjected to sonic treatment for about 1-60 minutes, preferably 2-30 minutes. However, it is apparent for the person skilled in the art that the mixing and
- 5 optionally sonic treatment time may vary from the time periods mentioned hereinbefore in dependence on the batch size of the prepared inhalation powder. After mixing and optionally sonic treatment the physiologically acceptable excipient is added. If according to a preferred embodiment of the invention only one portion of the suspending agent has been added in the process steps described hereinbefore,
- 10 the remaining suspending agent is added after addition of the excipient. After addition of the suspending agent the suspension thus obtained is stirred and optionally subjected to sonic treatment for about 1-60 minutes, preferably 2-30 minutes. However, it is apparent for the person skilled in the art that the mixing and optionally sonic treatment time may vary from the time periods mentioned
- 15 hereinbefore in dependence on the batch size of the prepared inhalation powder. Thereafter, the suspending agent is removed by means of filtration, centrifugation and/or evaporation; preferably by filtration or centrifugation. The residue thus obtained is dried at reduced pressure (preferably less than 300 mbar, more preferably between 20 - 200 mbar, most preferred between 30 - 100 mbar) for about
- 20 0.5 to about 12 hours, preferably for about 1 to about 6 hours, more preferably for about 1.5 to about 4 hours, either at room temperature or at elevated temperature (preferably more than 20°C, more preferably between 20 - 60°C, most preferred between 25 - 50°C). During the period of drying the powder is optionally turned around several times (for instance every 30 – 60 min). After drying the powder may
- 25 optionally be sieved. Before filling into the appropriate device or storage chamber or the like the resulting powder may optionally be exposed to certain environmental conditions (i.e. temperature: 10-60°C, preferably 20 – 45 °C; humidity 20-85% r.h., preferably 35 – 75% r.h.) for about 6 hours two about 3-4 days, preferably for about 10 - 72 hours, more preferably for about 12 - 60 hours.
- 30 One object of the invention concerns the tiotropium containing powdered preparations obtainable by the method of preparation described hereinbefore.
- Another object of the invention concerns the use of the tiotropium containing
- 35 powdered preparations according to the invention for the manufacture of a medicament suitable for inhalation. Another embodiment of the invention concerns the use of the tiotropium containing powdered preparations according to the invention for the manufacture of a medicament for the treatment of respiratory diseases, in particular asthma or COPD (chronic obstructive pulmonary disease).

The inhalable powders according to the invention may for example be administered using inhalers which meter a single dose from a reservoir by means of a measuring chamber (e.g. according to US 4570630A) or by other means (e.g. according to DE 36 25 685 A).

5

The following Examples serve to illustrate the present invention further without restricting its scope to the embodiments provided hereinafter by way of example.

Starting materials

10 In the Examples which follow, lactose-monohydrate (110M) is used as the excipient. The lactose-monohydrate used was obtained from Messrs DMV International, 5460 Veghel/NL (Product name Pharmatose 110M).

Preparation of tiotropium bromide monohydrate:

15 15.0 kg of tiotropium bromide as obtainable according to the methods disclosed in EP 418 716 A1 are added to 25.7 kg of water in a suitable reaction vessel. The mixture is heated to 80-90°C and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90°C and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70°C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3-5°C every 20 minutes to a temperature of 20-25°C. The apparatus is further cooled to 10-15°C using cold water
20 and crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction drier, the crystal slurry isolated is washed with 9 litres of cold water (10-15°C) and cold acetone (10-15°C). The crystals obtained are dried in a nitrogen current at 25°C over 2 hours.

Yield : 13.4 kg of tiotropium bromide monohydrate (86 % of theory)

25

30 The crystalline tiotropium bromide monohydrate obtainable using the method described above was investigated by DSC (Differential Scanning Calorimetry). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50-120°C can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at $230 \pm 5^\circ\text{C}$ can be put down to the melting of the substance. This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

The crystalline tiotropium bromide monohydrate obtainable using the method described above was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with $2.5\mu\text{mol}$ of tiotropium bromide monohydrate in 300 mg of KBr.

The following table shows some of the essential bands of the IR spectrum.

10

Wave number (cm^{-1})	Attribution	Type of oscillation
3570, 410	O-H	elongated oscillation
3105	Aryl C-H	elongated oscillation
1730	C=O	elongated oscillation
1260	Epoxide C-O	elongated oscillation
1035	Ester C-OC	elongated oscillation
720	Thiophene	cyclic oscillation

The crystalline tiotropium bromide monohydrate obtainable using the method described above was characterised by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R- 4-circuit diffractometer (Rigaku) using monochromatic copper K_{α} radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). The X-ray structural analysis carried out showed that crystalline tiotropium bromide monohydrate has a simple monoclinic cell with the following dimensions:

20 $a = 18.0774 \text{ \AA}$, $b = 11.9711 \text{ \AA}$, $c = 9.9321 \text{ \AA}$, $\beta = 102.691^\circ$, $V = 2096.96 \text{ \AA}^3$.

The crystalline tiotropium bromide monohydrate obtainable using the method described above is micronised by known methods, to bring the active substance into the average particle size which meets the specifications according to the invention.

25

The method of determining the average particle size of the various ingredients of the formulation according to the invention is described as follows.

A) Determining the particle size of micronised tiotropium bromide monohydrate:**5 Measuring equipment and settings:**

The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit:	RODOS dry disperser with suction funnel, Sympatec
10 Sample quantity:	50 mg - 400 mg
Product feed:	Vibri Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	40 rising to 100 %
Duration of sample feed:	15 to 25 sec. (in the case of 200 mg)
15 Focal length:	100 mm (measuring range: 0.9 - 175 µm)
Measuring time:	about 15 s (in the case of 200 mg)
Cycle time:	20 ms
Start/stop at:	1 % on channel 28
Dispersing gas:	compressed air
20 Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample preparation /product feed:

- 25 About 200 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then sprinkled finely over the front half of the vibrating channel (starting about 1 cm from the front edge). After the start of the measurement the frequency of the vibrating channel is varied from about 40 % up to 100 % (towards the end of the measurement). The sample should be fed in as continuously as possible. However, the amount of product should not be so great that adequate dispersion cannot be achieved. The time over which the entire sample is fed in is about 15 to 25 seconds for 200 mg, for example.

35 B) Determining the particle size of the excipient:**Measuring equipment and settings:**

The equipment is operated according to the manufacturer's instructions.

10

Measuring equipment: Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit: RODOS dry disperser with suction funnel, Sympatec
Sample quantity: 500 mg
5 Product feed: VIBRI Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel: 18 rising to 100 %
Focal length (1): 200 mm (measuring range: 1.8 - 350 µm)
Focal length (2): 500 mm (measuring range: 4.5 - 875 µm)
Measuring time: 10 s
10 Cycle time: 10 ms
Start/stop at: 1 % on channel 19
Pressure: 3 bar
Vacuum: maximum
Evaluation method: HRLD

15

Sample preparation /product feed:

About 500 mg of the test substance are weighed onto a piece of card.

Using another piece of card all the larger lumps are broken up. The powder is then transferred into the funnel of the vibrating channel. A gap of 1.2 to 1.4 mm is set

20 between the vibrating channel and funnel. After the start of the measurement the amplitude setting of the vibrating channel is increased from 0 to 40 % until a continuous flow of product is obtained. Then it is reduced to an amplitude of about 18%. Towards the end of the measurement the amplitude is increased to 100%.

Example 1:

- Crystalline tiotropium bromide monohydrate is weight into a mixing vessel (0.85 g). 400 ml of the suspending agent (n-hexane + 0.5% ethanol) are added. The 5 suspension is mixed (i.e. by means of a paddle mixer; mixing speed 200 rpm) and sonicated for 5 minutes. Mixing is continued without sonification for 5 minutes. 550 g Pharmatose 110M and 800 ml of the suspending agent (n-hexane + 0.5% ethanol) are added and mixing is continued for 5 minutes (mixing speed 450 rpm). After mixing is completed the suspending agent is removed by means of filtration. 10 The residue after filtration is dried in a vacuum (50-60 mbar) for 2 hours at 30°C. After drying the powder is sieved by means of a 0.5 mm sieve. The resulting powder is exposed to certain environmental conditions (temperature 21°C, 60 – 70% r.h), for 1-2 days before it is filled into the device.

Example 2:

Experiment conducted as described in example 1 with 1.7 g of crystalline tiotropium bromide monohydrate.

Example 3:

- 20 Crystalline tiotropium bromide monohydrate is weight into a mixing vessel (1.7 g). 400 ml of the suspending agent (n-hexane + 0.5% ethanol) are added. The suspension is mixed (i.e. by means of a paddle mixer; mixing speed 200 rpm) and sonicated for 5 minutes. Mixing is continued without sonification for 5 minutes. 550 g Pharmatose 110M and 400 ml of the suspending agent (n-hexane + 0.5% 25 ethanol) are added and the suspension thus obtained is mixed for 5 minutes (mixing speed 450 rpm) and sonicated. After mixing is completed the suspending agent is removed by means of filtration. The residue after filtration is dried in a vacuum (50-60 mbar) for 2 hours at 25°C. The resulting powder is exposed to certain 30 environmental conditions (temperature 21°C, 60 – 70% r.h), for 1-2 days before it is filled into the device.

Patent Claims

- 1) A method for preparing a physically stable and homogenous powdered preparation containing tiotropium in admixture with a physiologically acceptable excipient, characterized in that a tiotropium salt and a physiologically acceptable excipient are suspended in a suspending agent, in which the tiotropium salt and the physiologically acceptable excipient are essentially insoluble, and further characterized in that thereafter the suspending agent is removed.
- 10 2) Method according to claim 1, characterized in that the powdered preparation contains tiotropium in an amount of 0.001 to 2%.
- 15 3) Method according to claim 1 or 2, characterized in that the suspending agent is selected from the group consisting of alkanes, alcohols, ketones, mixtures of alkanes with alcohols and mixtures of alkanes with ketones.
- 20 4) Method according to one of claims 1 to 3, comprising the steps addition of a first portion of suspending agent to tiotropium salt, mixing and optionally sonic treatment of the suspension thus obtained, addition of the physiologically acceptable excipient, addition of another portion of suspending agent, mixing and optionally sonic treatment of the suspension thus obtained, removal of the suspending agent and drying of the residue thus obtained.
- 25 5) Method according to one of claims 1 to 4, characterized in that the powder/liquid ratio of the suspension is in a range of about 0.1 to about 2 g/ml,
- 6) Tiotropium containing powdered preparation obtainable according to the method according to one of claims 1 to 5.
- 30 7) Powdered preparation according to claim 6, characterized in that tiotropium is present in the form of the chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate thereof, preferably in form of the bromide.
- 35 8) Powdered preparations according to one of claims 6 or 7, characterized in that the physiologically acceptable excipients is selected from the group consisting of monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts or mixtures of these excipients with one another.

- 9) Powdered preparations according to claim 8, characterized in that the physiologically acceptable excipient is selected from the group consisting of glucose, arabinose, lactose, saccharose, maltose, trehalose, dextrane, sorbitol, mannitol, xylitol, sodium chloride, calcium carbonate and mixtures of these excipients with one another.
- 10) Use of a powdered preparation according to one of claims 6 to 9 for the manufacture of a medicament suitable for inhalation.
- 11) Use of a powdered preparation according to one of claims 6 to 9 for the manufacture of a medicament for the treatment of respiratory diseases.
- 12) Use of a powdered preparation according to claim 11, characterized in that the disease is asthma or COPD.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K31/46 A61K9/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 28979 A (SKYEPHARMA AG ; MUELLER WALZ RUDI (DE); KELLER MANFRED (DE)) 25 May 2000 (2000-05-25) example 6 ---	1-12
Y	WO 99 34778 A (LEIRAS OY ; LANKINEN TAPIO (FI)) 15 July 1999 (1999-07-15) example 2 page 9, line 15 -page 10, line 14 -----	1-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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